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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/971,344	11/17/1997	PHILP GOELET	04990.0008-2	4006

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EXAMINER
SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/26/2002 GL

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/971,344	GOELET ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *94-98,101-104,107-111 and 127-139* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *94-98,101-104,107-111 and 127-139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *61* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Group 1630, Art Unit 1634.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 03 July 2002 has been entered.

Drawings

3. Effective 03 May 2001, applicant may not hold in abeyance the submission of corrected formal drawings. Accordingly, applicant is required to submit corrected formal drawings in response to the Office action. See the PTO-948 that was attached to Paper No. 14, mailed 17 December 1996.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 94-98, 101-104, 107-111, and 127-139 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. Claims 94-98, 101-104, 107-111, and 127-139 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The quantity of experimentation need is great, on the order of several man-years and then with little, if any, reasonable expectation of success.

The Amount of Direction or Guidance Provided and The Presence or Absence of Working Examples

The specification identifies specific areas considered to be the invention and provides a series of examples to support certain embodiments. More specifically, the specification at pages 3-8 set forth in broad terms the following embodiments considered to be the invention:

- "The present invention is directed to molecules that comprise single nucleotide polymorphisms (SNPs) that are resent in mammalian DNA, and in particular, to equine and human genomic DNA polymorphisms." (Page 3, lines 27-30.)
- "The invention particularly concerns the embodiments wherein the mammal is a horse, and when the nucleic acid molecule has a nucleotide sequence selected from the group consisting of SEQ ID NO:(2n+1) [refer to Table 1], wherein n is an integer selected from the group consisting of 0 through 35, or wherein the sequence of the immediately 3'-distal segment includes a sequence selected from the group consisting of SEQ ID NO:(2n+2), wherein n is an integer selected from the group consisting of 0 through 35." (Page 4, lines 17-24.)
- "The invention also provides a method for determining the extent of genetic similarity between DNA of a target horse and DNA of a reference horse" (page 4, lines 33-35).
- "The invention further provides a method for determining the probability that a target horse will have a particular trait" (page 6, lines 12-13).
- "The invention further provides a method for creating a genetic map of a unique sequence equine polymorphisms" (page 6, lines 27-28).
- "The invention further provides a method for predicting whether a target horse will exhibit a predetermined trait," (page 7, lines 17-18).

- "The invention further provides a method for identifying a single nucleotide polymorphic site" (page 8, lines 1-2).
- "The invention also includes a method for interrogating a polymorphic region of a human single nucleotide polymorphism of a target human" (page 8, lines 20-22).

The specification sets forth the following examples:

- Example 1, pages 45-47, "Discovery of Equine Polymorphisms."
- Example 2, pages 47-50, "Characterization of Equine Polymorphisms."
- Example 3, pages 50-54, "Allelic Frequency Analysis of Equine Polymorphisms in Small Population Studies."
- Example 4, page 55, "[Equine] Parentage Testing."
- Example 5, pages 56-58, "[Equine] Identity Testing."
- Example 6, pages 58-62, "Analysis of Human SNP."

The Nature of the Invention

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The State of the Prior Art

The state of the prior art, based upon what was known in 03 November 1993, the filing date of he priority application, was extremely limited.

The Relative Skill of Those in the Art

The relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

The Breadth of Scope of the Claims

Claims 94-98 and 107-111 have sufficient breadth of scope so to encompass the generation of a genetic map for any and all life forms, without limit to the size of the nucleic acid being used and without restriction on the conditions under which the method is to be practiced.

Claims 101-104, 107-111, and 127-139 have sufficient breadth of scope so to encompass the creation of an association between any SNP variant and "any trait of interest." The "trait of interest" has, for purposes of examination, been considered to encompass not only physiological characteristics, but disease conditions, be they caused by a single gene or by a series of genes through unknown pathways, as well as improved growth and nutritional aspects of any plant or animal. Like the situation with claims 94-98 and 107-111 above, the claimed method has sufficient breadth so to encompass its being practiced under virtually any condition and where the sample is highly heterogeneous.

The claimed method is considered to encompass the use of hybridization reactions. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

The specification does not set forth in sufficient detail just how these art-recognized problems are to be overcome sans the skilled artisan having to resort to undue experimentation. As applicant has carefully and repeatedly indicated at the beginning of the specification, the invention contemplated by applicant at the time of filing, was directed to the use of specific markers in determining the parentage of thoroughbred horses. The claims now before the office are only tangentially related to such an invention. Clearly, the specification does not disclose in sufficient detail how any trait in any life form can be associated with one or more SNPs. Further, to practice such an invention, one would have to first know what the SNPs are for any species. In addition, given the scope of the claims, one would have to know the SNPs for every life form in the world to be capable of practicing the claimed invention to the fullest extent of the claims. Even at this late date, the art has not progressed to the point that one would be able to provide a comparison of all SNPs, be they of any breed of horse or for a human, much less for all other life forms. By not setting forth the reaction conditions and the starting materials that would be needed t practice the claimed invention to its fullest extent, applicant has shifted the burden of enablement from self to that of the public. Such shifting is both improper and creates an unfair

burden upon the public. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

7. Attention is directed to US2002/0086289 A1 where at page 2, left column it is stated:

> Hybridization-based methods for detecting many SNPs at once have been developed, but these methods generally lack robustness due to the difficulty in discriminating between

hybrids with exact matches and those with a single nucleotide mismatch (Gingeras et al., Genome Res. 8:435-438, 1988; Wan et al., Science 280:1077-1082, 1998). Some methods for genotyping SNPs only test for mutations at a single gene (Gingeras et al., 1998, supra). Other methods rely on multiplex PCR methodology, which suffers from irreproducibility. Thus, there is a need for a method for genotyping many SNPs at once that uses robust hybridization and amplification methodologies.

8. Attention is also directed to US2002/0076767 A1 where at page 4, last paragraph, bridging to page 5, it is stated:

> Those skilled in the art will appreciate that it is difficult to detect multiple SNPs by amplifying nucleic acid with specific primers because of the use of specific primers is costly and time consuming. On the other hand, random priming or semi-random priming, or priming to an adapter sequence is cheap and simple to amplify multiple nucleic acid sequences. However, because random priming or semi-random priming, or priming according to an adapter sequence is not specific, unwanted sequences may also been [sic, be] amplified. High concentrations of unwanted sequences can interfere [with] detection of multiple SNPs.

9. Attention is also directed to US 2002/0042061 A1 where at page 1, left column it is stated:

> [C]urrent genotyping technology based on polynucleotide hybridization often displays insufficient specificity to distinguish or identify single nucleotide polymorphisms. For instance, specific DNA strands/oligos containing one version of a specific SNP can hybridize not only to a perfectly matched complementary DNA but also to non-perfectly matched ones such as those [that] contain a second version of the specific SNP. Althought [sic] the hybridization is stronger between two perfectly complementary DNA strands than that between two non-perfectly complementary DNA strands (including those that have either a single or multiple base-pair-mismatch between two complementary strands). A single-base-pair difference is usually too small to render a high enough specificity for SNP scoring.

10. US 2002/00009736 A1, page 1, left column, penultimate paragraph, states in part:

> The presently available microarray biochip technology is certainly the method of choice to solve the problem of complexity, and the previously impossible task of defining a genetic signature for a unique person in a cohort with accuracy and speed that are impossible by the conventional diagnostic approach. (Emphasis added)

11. US 6,410,278 B1, column 1, penultimate paragraph, states:

> In practice, it is said that strict control of PCR is difficult with the difference of only one base given at the terminal of the primer. Accordingly, it is necessary to improve specificity in order to apply PCR to detection of SNPs.

12. US 6,297,018 B1, column 13, lines 44-49, state:

> Single-base mismatches are difficult to detect when the immobilized NDA probes are relatively long [when] compared to the mismatch, e.g., DNA chips often use 10-mers to 20-mers to achieve sequence uniqueness.

13. And attention s also directed to US 2002/0077775 A1 where, starting at page 1, right column, bridging to page 2, paragraph 15, where numerous issues confronting the assessment, application, and even utility of genetic maps is discussed.

14. While the art at the time of filing may not have recognized the innumerable difficulties that beset genetic mapping and methodologies used to identify and associate SNPs with any condition, trait, predisposition, etc., the art has advanced to where these issues are readily apparent and accordingly, one of skill in the art would be confronted with these very issues when attempting to practice the claimed invention. The instant claims place no restriction on the number of SNPs to be analyzed at a given time, nor on the manner in which the genetic map is produced, be it for an equine, a human, a plant or an insect. Clearly, the specification does not address these art-recognized difficulties and such non-disclosure effectively and inappropriately transfers the burden of enablement from applicant to the public. While some experimentation is permitted, and applicant need not disclose in excruciating detail each and every possible embodiment that one's claims may encompass, the specification must fully enable the full scope of that which is being claimed. Such has not happened here. The number and magnitude of the issues confronting one of skill in the art is of such magnitude that the specification has at best only points the skilled artisan in a general direction. Such disclosures, however, do not rise to

the level of an enabling disclosure. Accordingly, the amount of effort that would be required of the skilled artisan so to practice the full scope of the claimed invention is considered to constitute undue experimentation. For the above reasons, and in the absence of convincing evidence to the contrary, the claims are not considered to be enabled by the specification and as such, are rejected under 35 USC 112, first paragraph.

Response to argument

15. At page 4 of the response received 03 July 2002 argument is advanced one of skill in the art, using known technology, could resolve issues dealing with hybridization, citing Sambrook, J. et al. (Eds.), Molecular Cloning, Second Edition, Cold Spring Harbor Laboratory Pres, Cold Spring Harbor, New York (1989). This argument has been fully considered and has not been found persuasive. As set froth above, in the 5 years subsequent to the filing of the subject application and I the nearly 9 years since the asserted priority date, the art has if anything demonstrated how the detection and correlation of SNPs with any condition is wrought with innumerable difficulties, none of which are addressed in the publication of Sambrook et al., which predates the priority claim by approximately 4 years.

16. Also at page 4 of the response it is asserted that "the critical part of the presently claimed invention is directed to what is done with the SNP **after** it is identified, not how the SNP is identified." (Emphasis in the original) This argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection for while applicant may consider the "critical part" of their invention is what takes place subsequent to the detection of a SNP, the art clearly indicates that even identifying such is not nearly as straight forward as one would have

believed. Further, even with SNPs having been detected, the art further casts a pal over its usefulness; see US 2002/0077775 A1 at page 1, right column, bridging to page 2, paragraph 15.

17. Accordingly, and in the absence of convincing evidence to the contrary, the rejection is maintained.

18. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

19. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

22. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
July 23, 2002